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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/656,803 | 09/04/2003 | Warner C. Greene | UCAL-283 | 7086 |

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| EXAMINER | |
|---|---|
| BOESEN, AGNIESZKA | |
| ART UNIT | PAPER NUMBER |
| 1648 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 12/20/2006 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/656,803 | GREENE ET AL. | |
| | Examiner | Art Unit | |
| | Agnieszka Boesen | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *16-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The Amendment filed October 10, 2006 in response to the Office Action of July 11, 2006 is acknowledged and has been entered. Claims 1, 6, 11, 12 and 15 have been amended. Claims 1-15 are currently examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

### *Claim Objections*

Objection to claim 6 because of informalities **is withdrawn** in view of Applicant's amendments to the claims.

Objection to claim 6 because of typographical error **is withdrawn** in view of Applicant's amendments to the claims.

### *Claim Rejections - 35 USC § 103*

Rejection of claims 1-10, and 12-14 under 35 U.S.C. 103(a) as being unpatentable over Muthumani et al. (cited in the IDS) in view of Zlokarnik et al., (Science, 1998) **is maintained.**

Applicant's arguments have been fully considered but they are not persuasive. When pointing out to the illustrations in the Exhibits, it is assumed that Applicant intended to point to Exhibit C, for fusion and Exhibit D, for endocytosis, instead of Exhibits A and B, which were pertinent to Claim objections regarding CCF2.

Applicant argues that the reference by Muhatmani does not disclose detection of virion fusion where the detectable signal is not detectable prior to a complete viral fusion event, which is characterized by intracellular delivery of the contents of the viral capsid as required by the

present claims. Applicant further argues that if one used Vpr-GFP of Muhatmani, one could not distinguish between the fusion and endocytosis pathway and that one could not reasonably conclude from Muhatmani that virion fusion is either being detected or being detected independently of endocytosis.

Examiner points out that the retroviral virion (Vpr) of the current invention and the (Vpr) virion of Muhatmani are exactly the same. The virion of the current invention is used to infect primary cells such as lymphocytes from peripheral blood and Muhatmani's viron is used to infect normal human PBMCs (see page 181, Infectivity). Because the virion molecules and the cells being infected with the virions are exactly the same, the virions of Muhatmani and the virions of the present invention must enter the cell using the same pathway, either it is fusion or endocytosis. Thus, either fusion or endocytosis, or both are being detected in Muhatmani's method. The current claims do not require that virion fusion is being detected independently of endocytosis. The argument about not detecting endocytosis in the currently claimed method is moot, in the present case because, the current claims do not exclude endocytosis from being detected.

Applicant argues that the reference by Muhatmani does not disclose detection of virion fusion where the detectable signal is not detectable prior to a complete viral fusion event, which is characterized by intracellular delivery of the contents of the viral capsid as required by the present claims. Examiner respectfully disagrees. In both Muhatmani' s method and the method of the current invention the detectable signal is being detected using flow cytometry. Because in flow cytometry the treated sample, such in this case the cells infected with virions are being struck by the laser beam and the excitation of the label inside or on the surface on the cell

produces a detectable signal, the signal cannot be detected prior to the virion entering the cell either it happens trough fusion or endocytosis. For this reason also Muhatmani was able to detect the presence of the virion in the cells either the virion entered the cells trough fusion or endocytosis.

Applicant's argument regarding that CCF2 substrate is not able to cross the membrane forming either endocytic vesicle or the membrane of the intact virion, both of which would be needed for CCF2 to access the BlaM-Vpr fusion protein and for CCF2 to be cleaved by BlaM, and that for this reason the only way how the virion detected using CCF2 must have entered the cell is fusion, has been considered. It is acknowledged that CCF2 substrate has a selective means of entering the cell such fusion and not endocytosis. However the current claims do not recite that endocytosis is excluded. Furthermore, if the virion and the CCF2 enter the cells independently, because CCF2 enters the cell exclusively trough fusion does not exclude the virion entering the cell trough endocytosis. The CCF2 which entered the cell exclusively trough fusion may be able to be cleaved by beta-lactamase operably joined to the virion, wherein the virion has entered the cell trough either fusion or endocytosis. Thus it seems that the fact that the CCF2 enters the cells exclusively trough fusion does not prevent the virions entering the cells trough endocytosis. However, like Applicants pointed out because CCF2 enters the cells only trough fusion, only the virions that entered the cell trough fusion can be detected. Because the current claims do not exclude endocytosis the rejection is maintained.

Applicant's argument regarding that here is no motivation to modify Muhatmani's method to make the process selective for detecting fusion of an enveloped retrovirus to the target cell has been considered. Because Zlokarnik's uses CCF2 as a substrate for beta-lactamase, and

Zlokarnik teaches that CCF2 and its cleavage products, unlike GFP, diffuse throughout the cytosol (see page 88) and give a bright blue fluorescence, and CCF2 when it is cleaved, it results in free thiol group which almost completely quenches the fluorescence of fluorescein (see page 85), all factors making the CCF2 a recommendable substrate, one would have bee motivated to use CCF2 instead of GFP in Muhatmani's method. Thus, for the reasons discussed above, the current rejection is maintained.

Rejection of claims 11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muthumani et al. (cited in the IDS) in view of Zlokarnik et al., (Science, 1998) as applied to claim above, and further in view of Miyanohara et al. (US Patent 5,739,018) **is maintained.**

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues that US Patent 5,739,018 does not teach or suggest modifying the process of Muhatmani to make the process selective for detecting fusion of an enveloped retrovirus to a target cell. Examiner agrees that US Patent 5,739,018 does not teach or suggest modifying the process of Muhatmani to make the process selective for detecting fusion of an enveloped retrovirus to a target cell, because US 5,739,018 was cited to cure the deficiency of Muhatmani and Zlokarnik such as the retroviral vector pseuotyped with VSV-G. Because the US Patent '018 does teach the retroviral vector pseuotyped with VSV-G and this teaching cures the deficiency of Muhatmani and Zlokarnik, the current rejection is maintained.

*Conclusion*

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AB

Agnieszka Boesen, Ph.D.

12/14/06

Stacy B. Chen 12/16/06

STACY B. CHEN
PRIMARY EXAMINER